UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
ROGER BRIESEWITZ, GERALD R. CRABTREE, and THOMAS T. WANDLESS

Appeal 2007-2958
Application 09/716,842
Technology Center 1600

DECIDED: December 12, 2007

Before TONI R. SCHEINER, DONALD E. ADAMS, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellants appeal under 35 U.S.C. § 134 from the final rejection of claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56, all the claims remaining in the application. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse the rejection of the claims under 35 U.S.C. § 103(a), but remand the application to the Examiner for consideration of an issue discussed below.

DISCUSSION

Claim 16 is representative of the claimed subject matter:

16. A method for directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular space upon administration to a mammalian host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety comprising said drug or an active derivative thereof and a targeting moiety to an intracellular biodistribution modulating protein optionally joined by a linking group, wherein said drug moiety binds to a protein target and said targeting moiety is a peptidyl-prolyl isomerase ligand, and wherein said bifunctional molecule has a modulated biodistribution upon administration to said mammalian host as compared to a free drug control;

to direct said biodistribution of said drug upon administration to said host to an intracellular space as compared to a free drug control.

According to the Specification, the "bifunctional molecules of the subject invention are generally described by the formula: Z-L-X" (Spec. 6: 4-7), wherein "X is a drug moiety; L is [a] bond or [a] linking group; and Z is a targeting moiety" (*id.* at 6: 7-11). "The drug moiety X may be any molecule . . . that is capable of modulating a biological process in a living host, either by itself or in the context of the biodistribution modulating protein/bifunctional molecule binary complex" (*id.* at 6: 16-19), and includes "immunosuppressive agents" (*id.* at 14: 17). "Representative ligands capable of serving as the Z moiety of the bifunctional molecule include ligands for intracellular proteins, such as: peptidyl-prolyl isomerase ligands, e.g. FK506, rapamycin, cyclosporin A, and the like" (*id.* at 21: 3-5).

The claimed invention is a method of directing the distribution of a drug to an intracellular space, wherein the method comprises administering,

to a mammal, a bifunctional molecule consisting of (i) a drug moiety, and (ii) a peptidyl-prolyl isomerase ligand, wherein the drug is one that binds a protein, and the molecular weight of the bifunctional molecule does not exceed about 5000 daltons. *See e.g.*, Claim 16.

The Examiner rejected claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 under 35 U.S.C. § 103(a) as unpatentable over Forsgren[1] in view of Crabtree.[2]

Forsgren compares the tissue distribution of estramustine, a nitrogen mustard derivative of estradiol, with estradiol. "In contrast to estradiol, estramustine was found to be efficiently concentrated in the ventral prostate gland by a soluble [cytosol] protein" (Forsgren Abstract). "The presence of [the] nitrogen mustard moiety at position 3 of the [estradiol] was necessary for high-affinity binding to the protein" (*id.*). The Examiner acknowledges that estramustine does not have a peptidyl-prolyl isomerase ligand targeting moiety, and has a molecular weight exceeding 5000 daltons (Answer 3).

Crabtree describes a method "for the genetic engineering of host cells to render the cells and their progeny susceptible, in a regulated fashion, to programmed cell death (apoptosis) . . . useful as a means for eliminating [the] population of engineered cells" once the cells are no longer needed (Crabtree 3: 18-21). Briefly, cells are engineered to express "chimeric proteins contain[ing] at least one ligand-binding (or 'receptor') domain fused

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[1] Björn Forsgren et al., *Binding Characteristics of a Major Protein in Rat Ventral Prostate Cytosol That Interacts with Estramustine, a Nitrogen Mustard Derivative of 17β-Estradiol*, 39 Cancer Research 5155-5164 (1979).

[2] WO 95/02684, International Patent Application of Gerald R. Crabtree et al., published January 26, 1995.

to an action domain capable of initiating apoptosis within a cell" (*id.* at 3: 26-28). "[T]he various domains [of the chimeric proteins] are derived from different sources, and as such, are not found together in nature (i.e., are heterologous)" (*id.* at 3: 30-31). "[B]y way of example, . . . the chimeric protein[s] [are] capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline, or a steroid ligand" (*id.* at 4: 31-34). "[C]ells . . . contain[ing] [these] chimeric proteins . . . are responsive to the presence of a ligand which is capable of oligomerizing those chimera" (*id.* at 4: 18-20).

Engineered cells expressing the non-naturally occurring chimeric proteins may be administered to "animals, including humans, e.g. such that the cells produce a desired protein or other result within the animal" (Crabtree 9: 27-30). When elimination of the engineered cells from the animal is desired, administration of a "cell permeable multivalent ligand reagent which binds to the receptor domain [of the non-naturally occurring chimeric protein] leads to dimerization or oligomerization of the chimera . . . [which] triggers cell death" (Crabtree 3: 1-7).

"The oligomerizing ligands . . . are capable of binding to two (or more) of the receptor domains, i.e. to two or more chimeric proteins containing such receptor domains" (*id.* at 4: 6-8). "Examples of such ligands include those in which the [ ] moieties are the same or different and comprise an FK506-type moiety, a cyclosporin-type moiety, a steroid or tetracycline" (*id.* at 8: 21-23).

The Examiner contends "it would have been obvious . . . to substitute the estrogen targeting moiety [ ] linked to a drug as taught by Forsgren [ ] for any one of the binding pair as a targeting moiety such as peptidyl-prolyl isomerase ligand, i.e. FK506 . . . that binds to intracellular distributed receptor FKBP or cyclosporine that binds to intracellular distributed cyclophilin receptor" (Answer 5), "[g]iven the high binding affinity of the ligand receptor binding pair and the small size of the ligand as taught by [Forsgren]" (*id.*).

An invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known n the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). "Often, it will be necessary . . . to look to interrelated teachings of multiple [references] . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed[.]" *Id.* at 1740-41. "[T]his analysis should be made explicit" (*id.* at 1741), and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (*id.*).

In the present case, we find that the Examiner has not established that one of ordinary skill in the art would have had a reason to combine the references relied on in the manner claimed. In our opinion, the mere fact that Crabtree identifies FKBP and FK506, and cyclophilin and cyclosporin, as high affinity binding partners is not enough to suggest the substitution of FK506 or cyclosporin for either the estradiol moiety, or the nitrogen mustard

moiety (the actual targeting moiety) of Forsgren's estramustine, given the fact that Crabtree's objective is so dissimilar to Forsgren's.

Accordingly, we reverse the Examiner's rejection of the claims under 35 U.S.C. § 103(a) as obvious over the combined teachings of Forsgren and Crabtree.

REMAND TO THE EXAMINER

Although we have reversed the Examiner's rejection of the claims under 35 U.S.C. § 103(a), in our opinion, Crabtree is relevant to the patentability of the claimed invention for reasons other than those advanced by the Examiner.

"Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claims limitations, it anticipates." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). Moreover, "when considering a prior art method, the anticipation doctrine examines the natural and inherent results in that method without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005).

According to the present Specification, FK506 specifically binds FKBP, an "endogenous peptidyl-prolyl isomerase biodistribution modulating protein[ ]" (Spec. 26: 7-8), and is suitable as the targeting moiety of the instant bifunctional molecule (Spec. 21: 3-5). Also according to the Specification, the drug moiety of the bifunctional molecule "may be any molecule . . . that is capable of modulating a biological process in a living host," including "immunosuppressive agents" (Spec. 6: 16-17, and 14: 17).

We note that Cyclosporin A (or cyclosporine) binds the protein cyclophilin, and is defined as "an immunosuppressive drug [used] especially to prevent rejection of transplanted organs" (Merriam-Webster Medline Plus® Online Dictionary[3]). Moreover, it would appear that a heterodimer comprising FK506 and cyclosporin would have a molecular weight of less than 5000 daltons (Crabtree 33: 20-27).

Thus, Crabtree's description of administering a heterodimeric ligand "compris[ing] FK506 or an FK506-type moiety and a CsA or a cyclosporin type moiety" (*id.* at 34: 2-3) appears to anticipate the invention of claim 16, at the very least.

[3] Available at http://www.nlm.nih.gov/medlineplus/mlineplusdictionary.html

SUMMARY

The Examiner's rejection of claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 as obvious over the combined teachings of Forsgren and Crabtree is reversed. However, upon return of the application to the Technology Center, the Examiner is to consider whether Crabtree's disclosure of administration of an FK506-cyclosporin A heterodimer anticipates the invention, as defined by the present claims, and to take appropriate action based on the issues discussed above. Any further communication from the Examiner which contains a rejection of the claims should provide Appellants with a full and fair opportunity to respond.

REVERSED; REMANDED

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